PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below
International application No. PCT/EP2004/003245	International filing date *(day/month/year)* 26.03.2004
Priority date *(day/month/year)* 26.03.2003	
International Patent Classification (IPC) or both national classification and IPC C07K19/00, A61P31/12, A61P31/16	
Applicant APOGENIX BIOTECHNOLOGY AG	

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Irion, A

Telephone No. +49 89 2399-8174

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2004/003245

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-6,11,13,15-18 (all partially)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1-6,11,13,15-18 (all partially) are so unclear that no meaningful opinion could be formed *(specify)*:

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2004/003245

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2,3,5
	No:	Claims	1,4,6-21
Inventive step (IS)	Yes:	Claims	3
	No:	Claims	1,2,4-21
Industrial applicability (IA)	Yes:	Claims	1-21
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.

PCT/EP2004/003245

Item III

III.1 With respect to claims 1-6, 11, 13, and 15-18

Present claims 1-6,11,13,15-18 relate to compounds/products that are only defined by their functional feature of inhibiting the TRAIL ligand/TRAIL receptor system. Thus, present claims 1-6, 11, 13, and 15-18 are defined by the use of a compound having an inhibitory effect on the biological activity the TRAIL/TRAIL receptor system. The compound is defined entirely by its effect on said biological activity. Thus, said claims are unclear within the meaning of Article 6 PCT because in order to determine the scope of the claims the skilled person would have to test all known and yet unknown substances to detect their effect on the Trail ligand/Trail receptor system. This screening programme represents certainly an undue burden. Moreover, in the absence of a precise definition of the nature of the biological activity of the TRAIL/TRAIL receptor system which in view of the complexity of cell biochemistry may show itself in many different ways, the measurement of whether or not a given compound show an inhibitory effect, would not be straightforward to the skilled person. In the present case, the claims lack clarity, that a meaningful search and thus examination over the whole of the claimed scope is impossible. Consequently, the search, and thus the examination, has been carried out for those parts of the claims which appear to be explicity and unambigously disclosed in the application, namely those parts relating to the compounds/products being the inhibitors:

1. an inhibitory anti-TRAIL-ligand-antibody as defined in claim 7
2. a soluble TRAIL-receptor molecule as defined in claim 7
3. an inhibitory anti-TRAIL receptor-antibody as defined in claim 12
4. an inhibitory TRAIL ligand fragment as defined in claim 12
5. anti-sense molecules, RNAi molecules, ribozymes as defined in claim 14
6. antibodies which are specifically directed against the Death domain of TRAIL-R1, TRAIL-R2 or FADD as mentioned on p. 4 l. 21-25 and claim 16
7. Caspase inhibitor being Z-VAD-FMK as disclosed in the Example on p. 15 l. 5-9.

Item V

V.1 Reference is made to following documents

D1: US6072047 (C. RAUCH & H. WALCZAK) 06 June 2000 (2000-06-06)
D2: US6284236 (S.R. WILEY & R.G. GOODWIN) 04 September 2001 (2001-09-04)

D3: WO9909165 (IDUN PHARMACEUTICALS, INC) 25 February 1999 (1999-02-25)

D4: WO0066156 (HUMAN GENOME SCIENCES, INC) 09 November 2000 (2000-11-09)

D5: WO02097033 (HUMAN GENOME SCIENCES, INC) 05 December 2002 (2000-12-05)

D6: M.J. RAFTERY ET AL.: 'Targeting the function of mature dendritic cells by human cytomegalovirus: a multilayered viral defence strategy', IMMUNITY, December 2001 (2001-12), vol. 15, pages 997-1009

D7: W. WURZER: 'Die Rolle des Transkriptionsfactors NF-kB in Influenza-A-Virus infizierten Zellen', Dissertation zur Erlangung des naturwissenschaftlichen Doktorgrades der Bayrischen Julius-Maximillians-Universität Würzburg, Publikationsdatum 27.06.2003

D8: W.J. WURZER ET AL: 'Caspase 3 activation is essential for efficient influenza virus propagation', THE EMBO JOURNAL, 02 June 2003 (2003-06-02), vol. 22 no. 11, pages 2717-2728

V.2 Novelty (Article 33(2) PCT)

V.2.1 With respect to claims 1, 4, and 6-21

Document D1 describes inhibiting soluble TRAIL-receptor polypeptides (col. 1 l. 57-63, col. 4 l. 52-56, Example 7) expressed as a Fc-fusion protein (col. 12 l. 60 - col. 13 l. 12). Furthermore, antagonistic anti-TRAIL-R antibodies (col. 2 l. 11-14, col. 20 l. 25 - col. 21 l. 34, Example 4) and antisense molecules (col. 22 l. 36 - col. 23 l. 39) are described. Moreover, a screening method of testing the TRAIL-mediated apoptosis blocking activity of a TRAIL-R polypeptide is disclosed (col. 15 l. 29-36). The use of TRAIL-R to reduce TRAIL-mediated death of T cells in HIV-infected patients is described (col. 18 l. 42 - col. 19 l. 40). Furthermore, caspase inhibitors and FADD-DN blocking TRAIL-induced apoptosis are disclosed (Example 8). Pharmaceutical compositions comprising the molecules described above together with carriers, diluents and/or adjuvants is also disclosed in D1 (col. 19 l. 41-56, col. 21 l. 47-51). Further active ingredients, such an agent that blocks FasL/Fas interactions, are comprised in said compositions (col. 19 l. 20-40).
Therefore, the subject-matter of claims 1, 4, 6-21 is not considered novel in the sense of Article 33(2) PCT.

Document D2 describes inhibiting TRAIL-Fc fusion proteins (col. 11 l. 48 - col. 12 l.

19), anti-TRAIL antibodies (col. 30 l. 15 - col. 31 l. 58, Example 4) and antisense molecules (col. 29 l. 10 - col. 30 l. 14). Such inhibiting molecules may be used in diseases in which excessive apoptosis occurs, e.g. HIV infections, infectious mononucleosis, and cytomegalovirus infection (col. 24 l. 53-62). An assay for identifying blocking antibodies is described measuring the viability of cells (Example 12). Pharmaceutical compositions comprising the molecules described above together with carriers, diluents and/or adjuvants is also disclosed in D2 (col. 32 l. 16-20). Further active ingredients, such an agent that blocks FasL/Fas interactions, are further comprised in said compositions (col. 32 l. 5-15).
Therefore, the subject-matter of claims 1, 4, 6, 7, 11-13, and 17-21 is not considered novel in the sense of Article 33(2) PCT.

Document D3 describes the TRAIL-receptors DR5 (TRAIL-R2) and TRAIL-R3 which are used to raise antibodies against these molecules (p. 23 3rd paragraph - p. 24 1st paragraph) and which are also used in bioassays to identify agonists and antagonists thereto (p. 3 3rd paragraph, p. 27 5th paragraph - p. 31 1st paragraph). The anti-DR5 and anti-TRAIL-R3 antibodies are used to modulate the biological effect of DR5 or TRAIL-R3 in vivo (p. 4 2nd paragraph, p. 24 4th paragraph - p. 25 1st paragraph). DR5 splicing variants show inhibiting activity of apoptosis induced by TRAIL (p. 7 2nd paragraph). Active fragments of an DR5 or TRAIL-R3 extracellular domain are disclosed (p. 11 2nd paragraph). Antisense oligonucleotides preventing translation of the receptor mRNA are disclosed (p. 18 3rd paragraph - p. 19 4th paragraph).
Therefore, the subject-matter of claims 19-21 is not considered novel in the sense of Article 33(2) PCT.

Document D4 describes inhibitory TRAIL-R2-Fc fusion proteins (corresponding to the extracellular domain of TRAIL-R2) and anti-TRAIL-R antibodies which may be used in the treatment of HIV infections thereby blocking the HIV-induced apoptosis of T cells (p. 67 l. 16 - p. 68 l. 14, p. 100 l. 6 - p. 111 l. 2, p. 131 l. 9-14). Antibody based therapies in which the antibodies are administered to an animal, preferably a mammal such as a non-human primate, are disclosed (p. 127 l. 19 - p. 128 l. 5, p. 153 l. 15-28). Further antagonists of the invention are useful for enhancing T-cell mediated immune responses, as well as preventing or treating diseases associated with decreased T-cell proliferation such as AIDS (p. 132 l. 1-14, p. 140 l. 10 - p. 141 l. 31). Agonists and/or antagonists of TRAIL/Trail-R interaction may be used as a vaccine adjuvant to enhance anti-viral immune responses, e.g. against AIDS, meningitis, Influenza A and B (p. 147 l. 18 - p. 148 l. 4). Antagonists of TRAIL-R2

include further antisense nucleic acids, ribozymes or soluble forms of the DR5 receptors (p. 152 l. 16-17, p. 161 l. 10 - p. 163 l. 19). Furthermore, screening methods for identifying agonists and antagonists of TRAIL-R2 activity are disclosed (p. 154 l. 28 - p. 156 l. 25). A composition comprising the above-mentioned molecules comprises further adjuvants (p. 176 l. 20-21) and other therapeutic agents (p. 177 l. 14-27).
Therefore, the subject-matter of claims 1, 4-14, and 17-21 are not considered novel in the sense of Article 33(2) PCT.

Document D5 describes the use of agonistic and antagonistic antibodies against TRAIL-R4 in the treatment of AIDS, and viral infections such as influenza virus infection (paragraph [0319]-[0323]). Antagonistic antibodies are used to treat HIV infection. Therefore, the subject-matter of claims 1, 4, and 12 is not considered novel in the sense of Article 33(2) PCT.

Document D6 describes the used of TRAIL-R2-Fc fusion protein (extracellular portion of TRAIL-R2) for the inhibition of TRAIL-induced apoptosis of activated T lymphocytes mediated by dendritic cells infected by CMV (abstract, p. 1005 right-hand col. 3rd paragraph - p. 1006 left-hand col. 3rd paragraph, p. 1007 right-hand col. 4th paragraph). The induction of apoptosis in activated T cells is considered as a viral defense mechanism (abstract and p. 999 left-hand col. 1st paragraph). Therefore, the subject-matter of claims 1, 6-10, and 17 is not considered novel in the sense of Article 33(2) PCT.

Thus, claims 1 and 4-21 do not meet the requirements of Article 33(2) PCT.

V.2.2 With respect to claims 2 and 3

None of the documents cited above describe the subject-matter of claims 2 and 3. Therefore, said claims are considered novel in the sense of Article 33(2) PCT.

V.3 Inventive step (Article 33(3) PCT)

V.3.1 With respect to claim 2

Since no experimental results are given in the application as originally filed supporting the alleged effect of a treatment success against Borna disease virus and the results of the influenza virus experiments do not allow a direct transfer to BDV, the subject-matter of claim 2 is not considered inventive in the sense of Article 33(3) PCT.

V.3.2 With respect to claim 3

The subject-matter of claim 3 is neither disclosed nor suggested in the documents cited above. Furthermore, the application as originally filed shows experimental results of an 80% decrease of influenza virus production in the presence of TRAIL-R2-Fc. Therefore, the subject-matter of claim 3 is considered inventive in the sense of Article 33(3) PCT.

V.4 Industrial applicability (Article 33(4) PCT)

V.4.1 With respect to claims 1-21

The subject-matter of claims 1-21 appears to be susceptible of industrial application.

Item VI

VI.1 With respect to documents D7-D8

The examination report has been based on an assumed valid priority for the present application. Should the priority of the present application not be valid, the above cited documents D7-D8 would be relevant with respect to novelty and inventive step (Article 33(2) and (3) PCT).